Nonsense-Mediated RNA Decay Influences Human Embryonic Stem Cell Fate.

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Authors: Chih-Hong Lou, Jennifer Dumdie, Alexandra Goetz, Eleen Y Shum, David Brafman, Xiaoyan Liao, Sergio Mora-Castilla, Madhuvanthi Ramaiah, Heidi Cook-Andersen, Louise Laurent, Miles F Wilkinson

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Public Summary:
Lou et al. addresses an age-old question – how does a human embryo transform itself into a human body comprised of multiple complex organ systems? Most studies have focused on the role of DNA-binding proteins called “transcription factors” in this developmental process. By regulating the synthesis of messenger RNA (mRNA) from the DNA template, transcription factors act as key control switches during development. In Lou et al., the role of an alternative mechanism—selective mRNA decay—is studied. This is biologically relevant, as mRNA decay is just as important as mRNA synthesis in determining the amount of mRNA (and hence the amount of encoded protein) that accumulates in a cell. A highly conserved pathway known to selectively degrade certain mRNAs, while retaining others, is called nonsense-mediated RNA decay (NMD). It was previously shown by the Wilkinson laboratory that NMD magnitude is downregulated in neural stem cells to allow them to become mature neurons. This downregulatory mechanism is critical, as it allows critical mRNAs important for neural differentiation to be stabilized. Now, this same laboratory has found that NMD is also downregulated in human embryonic stem (hES) cells when they differentiate into definitive endoderm, the primary germ layer that ultimately gives rise to cells in several organ systems, including lung, thyroid, and digestive cells. Through a series of gain- and loss-of-function experiments, Lou et al. show that NMD must be downregulated to efficiently generate definitive endoderm. Indeed, depletion of NMD factors is sufficient to elicit the generation of definitive endoderm from hES cells. In contrast, NMD was found to be upregulated and necessary for hES cell differentiation into mesoderm, the primary germ layer that gives rise to muscle and cartilage cells, among other cell types. Evidence was obtained that NMD has this yin-yang effect by altering the levels of mRNAs encoding specific cell signaling molecules. This research has the potential to impact regenerative medicine by defining new ways to efficiently generate specific cell types from hES cells.

Scientific Abstract:
Nonsense-mediated RNA decay (NMD) is a highly conserved pathway that selectively degrades specific subsets of RNA transcripts. Here, we provide evidence that NMD regulates early human developmental cell fate. We found that NMD factors tend to be expressed at higher levels in human pluripotent cells than in differentiated cells, raising the possibility that NMD must be downregulated to permit differentiation. Loss- and gain-of-function experiments in human embryonic stem cells (hESCs) demonstrated that, indeed, NMD downregulation is essential for efficient generation of definitive endoderm. RNA-seq analysis identified NMD target transcripts induced when NMD is suppressed in hESCs, including many encoding signaling components. This led us to test the role of TGF-beta and BMP signaling, which we found NMD acts through to influence definitive endoderm versus mesoderm fate. Our results suggest that selective RNA decay is critical for specifying the developmental fate of specific human embryonic cell lineages.